External validation of a risk model of febrile neutropenia occurrence in patients with non-Hodgkin lymphoma

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ORIGINAL ARTICLE

External validation of a risk model of febrile neutropenia occurrence in non-Hodgkin lymphoma patients

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ABSTRACT

Febrile neutropenia (FN) is a common and serious complication of chemotherapy treatment. Clinical risk models may help identify high risk FN patients but must undergo external validation before implementation in medical practice. Therefore, this study externally validated previously published clinical models of FN occurrence during chemotherapy in 240 non-Hodgkin lymphoma patients by using an independent observational dataset (N=1829). The models demonstrated predictive ability, and validation criteria for predicting any cycle FN were partially met but a larger than expected decrease in performance was noted (area under the receiver operating characteristic curve was 0.71 in the validation dataset and 0.83 in the training dataset). Age, weight, baseline white blood cell counts and planned chemotherapy parameters were confirmed to predict FN risk. Chemotherapy dose reductions, dose delays and colony-stimulating factor use were confirmed as risk modifiers during treatment. Further work is needed to improve the predictive ability of FN risk models.

INTRODUCTION

Febrile neutropenia (FN) is a serious and frequent complication in cancer patients receiving chemotherapy that may necessitate hospitalizations and intravenous antibiotic treatment, affect treatment delivery and treatment success and increase short-term mortality [1-3]. In addition to the clinical consequences, FN in cancer patients can cause substantial hospitalization costs [4,5]. The majority of aggressive non-Hodgkin lymphoma (NHL) patients receive chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) with or without rituximab (R) [6]. CHOP chemotherapy with a cycle length of 21 days showed FN rates of 20% or more and R-CHOP chemotherapy with a cycle length of 21 days showed rates close to 20%, in NHL patients under European routine practice conditions [7,8]. Dose dense (R-)CHOP regimens with a cycle length of 14 days have a substantially higher risk of neutropenic events and require routine administration of prophylactic colony-stimulating factor (CSF) [8,9].

Prophylactic CSF use is recommended by the European Organisation for Research and Treatment of Cancer (EORTC) and other international guidelines [8-11] if the FN risk of a planned chemotherapy regimen is 20% or higher. Effective targeting of CSF prophylaxis is particularly important for chemotherapy regimens with an FN risk of 10-20%, when patient risk factors must be incorporated into clinical decision making [8,9]. Antibacterial and antifungal prophylaxis have recently been recommended for neutropenic patients expected to have less than 100 neutrophils per µL for more than a week, or other risk factors for complications [12]. In patients with incurable cancer, FN risk may influence decisions on the continuation and choice of chemotherapy as well as treatment intensity. Numerous patient risk factors have been reported to increase the risk of FN including older age, low baseline blood cell counts, low serum albumin, anemia, abnormal bone marrow, increased lactate dehydrogenase (LDH), renal comorbidity, cardiovascular or hepatic disease, full dose or high-risk planned chemotherapy regimen and lack of CSF prophylaxis; and several neutropenia risk models in different cancers have been proposed [7,13-15]. Clinical risk models of FN occurrence with good predictive ability could play an important role in quantifying individual FN risk in cancer patients and targeting appropriate measures to high risk patients [14].

We previously developed risk models of FN in first and any cycle of chemotherapy using data on 240 NHL patients from the INC-EU (Impact of Neutropenia in Chemotherapy – European Study Group) Prospective Observational European Neutropenia Study [16]. The resulting models showed good test characteristics and we saw little degradation of model performance in internal 10-fold cross-validation, an approach that can be used if the available database is limited. However, before risk models can be put to clinical use they should undergo external validation in an independent dataset [17], but this occurs rarely [18]. Few neutropenia risk

models have been validated using split-sample methods, i.e. dataset is randomly split-up into training set and validation set [19,20] and we are aware of only one partial validation using an independent dataset [21]. These more far-reaching validation efforts involved mixed tumor or breast cancer populations. Some of the associations found may hence be spurious or not applicable to the NHL setting.

Therefore, we aimed to assess the ability of the INC-EU models to predict the FN risk of NHL patients on external data, using the independent, observational IMPACT NHL database. If successful, the INC-EU models might help identifying high risk versus low risk patients in clinical practice.

MATERIALS AND METHODS

Characteristics of the INC-EU study and model

The INC-EU Prospective Observational European Neutropenia Study was conducted in Belgium, France, Germany, Spain and the UK to assess the incidence and predictors of neutropenic events and reduced chemotherapy delivery for breast cancer and lymphoma patients undergoing chemotherapy [7,16,22]. The methodology of this study has been previously described [7]. IMPACT NHL (ClinialTrials.gov: NCT00903812) was a multi-centre, retrospective and prospective, observational study of NHL patients receiving (R-)CHOP chemotherapy. A total of 1864 patients were enrolled in 14 European countries and Australia to evaluate FN risk-assessment, FN occurrence and CSF use in routine medical practice; 1829 patients met all eligibility criteria [23,24]. Eligibility criteria were broad in both studies. Near-identity of patient characteristics was not required for the purpose of external validation as risk models should perform well in populations with partially different characteristics; otherwise their scope would be too narrow.

The characteristics of the INC-EU models have been previously published [16]. Covariates were selected based on clinical and statistical grounds. Clinically relevant risk factors significantly associated with FN in cycle 1 of chemotherapy were older age, increasing planned cyclophosphamide dose, increasing planned etoposide dose, previous chemotherapy, recent infection and low baseline albumin. The same factors, with the exception of previous chemotherapy and low baseline albumin, were also predictive of any cycle FN occurrence. Higher weight and prophylactic CSF use were protective factors in both models; antibiotic prophylaxis had no significant effect and was therefore excluded [16]. The following additional factors were statistically significant predictors of risk of any cycle FN: low baseline absolute neutrophil count (ANC) or white blood cell count (WBC), high baseline alkaline phosphatase, cardiovascular comorbidity and increasing planned cytarabine dose. Chemotherapy dose reductions and dose delays before an FN event occurred decreased the

risk of FN. The INC-EU models demonstrated good apparent predictive ability; apparent in that performance was assessed directly in the dataset used to develop the models. Predictive ability was only slightly reduced under 10-fold cross validation conditions.

Feasibility of comparing the INC-EU and IMPACT NHL studies was assessed. In the INC-EU study, FN was defined as a temperature of ≥38.0˚C in conjunction with an ANC $<0.5\times10^9$/L or WBC $<1.0\times10^9$/L [16]. IMPACT NHL used a slightly broader definition as a neutrophil count $\leq1.0\times10^9$/L was sufficient if predicted to fall below $<0.5\times10^9$/L [23,24]. The exact time points of FN events were not directly available from the IMPACT NHL data. CSF use in the relevant chemotherapy cycles was therefore assumed to precede the FN event if it started on cycle days 1-7. Definitions of patient demographics or characteristics (used as covariates in the models) were reasonably similar or could be aligned by applying INC-EU definitions to IMPACT NHL.

Covariates representing high baseline alkaline phosphatase (used in the INC-EU model of FN risk in any cycle) and recent infection were not available from the IMPACT NHL dataset. A sensitivity analysis using the INC-EU dataset investigated the effect of omitting these variables and showed that they contributed little to the risk models' overall predictive ability (area under the receiver operating characteristic (ROC) curve and test characteristics remained stable when they were excluded, as did the regression coefficients estimated for the other predictor variables). However, the most important predictors of FN such as age, previous chemotherapy, planned chemotherapy dose, CSF use, and baseline neutrophil counts were available for both study populations or could be derived from the IMPACT NHL dataset.

External validation of the INC-EU models

The external validation followed a double approach. First, we assessed the performance of the INC-EU risk models when applied to the IMPACT NHL database. The logistic regression coefficients constituting the INC-EU models were combined with covariate values from the IMPACT NHL population. Linear predictors for risk of FN in cycle 1 and in any cycle were calculated for 1818 and 1675 IMPACT NHL patients, respectively, with no missing values for the relevant variables, and converted to predicted probabilities. These predicted probabilities for FN were compared with the patients' actual FN experience (occurrence yes versus no) in the first or any cycle of chemotherapy. Predictive ability was assessed by calculating the area under the ROC curve and test characteristics such as sensitivity, specificity, positive predictive value (PPV, proportion of patients classified as high risk by the model who actually have an event) and negative predictive value (NPV, proportion of patients classified as low risk by the model who actually have no event). Test characteristics were calculated at the optimal cut-off (i.e. the cut-off where sensitivity equals specificity) observed for both the INC-

EU and IMPACT NHL datasets, and at a cut-off of 0.5. We pre-specified that the risk models would be regarded as formally successfully validated if the sensitivity and specificity were no less than the observed values for the INC-EU dataset minus 10%, and if the area under the ROC curve was greater than 0.75 (compared to 0.86 and 0.83 for the INC-EU dataset), based on the recommendations of published validation reports [25-27].
Second, to generate supplementary information, logistic regression coefficients were re-estimated using the IMPACT NHL database, i.e. the effects deemed significant in the INC-EU models were re-estimated from the IMPACT NHL data and compared with the original regression coefficient estimates.

RESULTS

The INC-EU risk model was based on 240 NHL patients and the IMPACT NHL full analysis set used for validation included 1829 NHL patients. As presented in Table I, the INC-EU and IMPACT NHL populations showed similar treatment and patient characteristics. FN occurred in cycle 1 in 21 (9%) and in 127 (7%) patients in the INC-EU and IMPACT NHL studies, respectively, and was reported in any cycle FN in 53 (22%) and in 331 (18%) patients, respectively.

Ability of the INC-EU models to predict FN in the IMPACT NHL database

The INC-EU risk models predicted the occurrence of FN in cycle 1 and in any cycle in IMPACT NHL patients (Table II). For FN in cycle 1, the area under the ROC curve was 0.64 (95% confidence interval [CI] 0.59-0.69) (Figure 1a) and 0.71 (CI 0.68-0.75) for FN in any cycle (Figure 1b). In both cases, the lower confidence limit for the area under the ROC curve was significantly higher than 0.5, i.e. above the value that would indicate no predictive ability. Overall, 1074 out of 1818 patients (59%) were classified correctly in the first cycle; 75 (4%) positively predicted patients experienced FN and 999 (55%) negatively predicted patients did not experience FN. Correct predictions in any cycle FN were higher; overall, 1113 patients out of 1675 (66%) were correctly classified; 201 (12%) positively predicted patients experienced FN and 912 (54%) negatively predicted patients did not experience FN. These results were calculated using the optimal cut-off observed for the IMPACT NHL dataset (0.014 for FN in cycle 1 and 0.089 in any cycle). When the other cut-offs were used, test characteristics shifted towards lower sensitivity and higher specificity. When using a cut-off of 0.5, sensitivity was very low in the first cycle model (2%) and low in the any cycle model (18%), specificity was very high in both models (99% and 97%) and the NPV was 93% in the first cycle model and 85% in the any cycle model.

Re-estimation of model parameters from the IMPACT NHL database

When the model parameters of the first cycle INC-EU [16] FN model were re-estimated using the IMPACT NHL dataset, all effects maintained their original direction (with the exception of missing baseline albumin, a category that was introduced not to lose too many observations, as baseline albumin was not recorded for all patients), but some effect sizes were substantially reduced (e.g. age, previous chemotherapy) and the majority of effects were not statistically significant (Table III). The re-estimated model obtained an apparent area under the ROC curve of 0.67 (CI 0.62-0.72) compared to 0.86 (CI 0.79-0-94) for the original INC-EU model of cycle 1 FN [16].

In the any cycle model, all effects maintained their original direction and in this case effects remained statistically significant (with the exception of previous chemotherapy and cardiovascular comorbidity). Again, most effect sizes were reduced (Table III). Planned cycle length, distinguishing dose-dense ([R-]CHOP-14) from standard chemotherapy delivery ([R-]CHOP-21), was not statistically significant in the INC-EU any cycle model but was statistically significant in the re-estimated model. The re-estimated model obtained an apparent area under the ROC curve of 0.74 (CI 0.70-0.77) compared to 0.83 (CI 0.76-0.90) for the corresponding INC-EU model of FN in any cycle [16].

Ad Hoc analysis of baseline albumin

In the original INC-EU models [16], the effect of low baseline albumin was significant in the FN in cycle 1 model but failed to reach significance in the FN in any cycle model. In an unplanned *ad hoc* analysis it was assessed whether low baseline albumin would be predictive of FN in any cycle in the IMPACT NHL data. The addition of low baseline albumin as a covariate to the IMPACT NHL models confirmed an effect of low baseline albumin on the incidence of FN in any cycle. The resulting coefficient (OR = 1.80, CI 1.3-2.5) was highly significant. In light of this, the impact of including low baseline albumin in the published INC-EU model (FN in any cycle) on the ability to predict FN in the IMPACT NHL dataset was investigated. Little impact of adding low baseline albumin was seen and consequently the predictive ability of the modified algorithm was not substantially increased in comparison to the algorithm resulting from the published INC-EU model.

DISCUSSION

Models that identify and quantify individual FN risk factors can aid clinical practice and facilitate adherence to guideline recommendations. Our risk models for NHL patients demonstrated some ability to predict FN occurrence in cycle 1 and in any cycle of chemotherapy, in the entirely independent IMPACT NHL database. The observed high NPV (≥90%) relative to PPV is common to many risk models, here reflecting the ratio of patients without *versus* with FN (e.g., an overall FN incidence in the IMPACT study of 18% translates

to a NPV of 82% in the absence of modelled risk assessment). However, formal pre-defined criteria for successful validation were not met for the cycle 1 model. The any cycle model, met criteria for sensitivity and specificity but not those for area under the ROC curve. The overall decrease in performance in the external validation dataset compared to the training dataset was larger than expected. Application to individual patients in routine practice would probably not achieve a sufficiently precise prediction of actual FN risk.

A number of the covariates used in the original INC-EU models were confirmed to be important predictors of FN and are likely to be important elements of future (more refined) prediction models. These covariates included age, weight, low baseline ANC or WBC, planned chemotherapy cycle length and planned cyclophosphamide dose (where applicable). Chemotherapy dose reductions and delays, and CSF use were confirmed as important modifiers of FN risk during the course of chemotherapy. They can decrease the risk of FN in subsequent cycles with impact on the overall risk, but their use is often triggered by the observed or anticipated FN risk in early cycles. Effects of previous chemotherapy (incidence of previous chemotherapy was <10% in both the INC-EU and the IMPACT NHL data) and cardiovascular comorbidity could not be confirmed The capture of cardiovascular comorbidity data in IMPACT NHL was not well standardized; only system organ class comorbidity data were collected without including further details on specific disease states. Consequently, the potential for correctly assessing the impact of these covariates may have been limited. Low albumin is representative of poor nutritional condition. An unplanned extension of our external validation analyses suggested that low baseline albumin may be an influential contributor to the risk of FN. Although its impact on the predictive ability of the models was limited, clinical decision making should possibly take this element into account when assessing patient risk factors. The true effect of low baseline albumin warrants further investigation.

The predictive ability of the original INC-EU models of FN occurrence, when applied to independent lymphoma datasets, is unlikely to be sufficient for effective prediction. As validated risk models of FN occurrence in NHL patients and other cancer patients are rare, there is a lack of materials our results can be compared with. The apparent predictive ability of our models resembled that of a model recently published by Lyman, *et al.,* in which risk of severe and febrile neutropenia in cycle 1 was assessed in patients with solid tumors and malignant lymphomas [20]. These authors reported an apparent NPV of 96% and PPV of 34%. Within-study 2:1 random split-sample validation resulted in a slightly increased PPV (36%) but lower NPV (93%). The fact that our validation study used data on NHL patients enrolled into an entirely different study may explain the much larger performance change seen in our case [20,28]. A risk model developed by López-Pousa, *et al.* [29] for first cycle chemotherapy-induced neutropenia in 1194 patients with solid tumors had slightly lower

apparent predictive ability (PPV of 17% and NPV of 94%) than our model. To our knowledge, this model has not been validated externally. The observed differences in model performance under different conditions and especially the difference in performance change that may result from the use of random split-sample validation *versus* true external validation confirms the importance of the latter approach before risk models are put to clinical use.

Using prospectively collected data (in the INC-EU study and part of the IMPACT NHL study) to develop and validate prognostic models may add strength as such data may be more reliable than retrospectively collected data. Possible limitations of our work include the small training dataset sample size (N = 240), the mixture of first line and relapsed chemotherapy patients with different treatment histories (although ≤10% in both datasets had previous chemotherapy) and treatment intensity, slight differences in some definitions between the IMPACT NHL study and the INC-EU study and unavailability of two covariates of limited relevance in IMPACT NHL. However, we consider only the limited size of the training set has possibly contributed to the decrease in performance. Another possible explanation could be the lack of accounting for other, unknown prognostic covariates such as biological or genetic risk factors [30]. In addition, correct representation of the neutropenic potential of combination chemotherapy regimens remains a challenge. The dosage of the individual components is often correlated (e.g. patients with higher body surface area get a proportionally higher dose of each substance). This makes it difficult to correctly estimate the risk associated with each individual agent. Moreover, agents are used in different combinations (although not so much here where CHOP was predominantly used); to our knowledge, their interaction has not been systematically studied in routine practice populations, with a focus on implications for FN risk. An additional issue that arises when risk models are put to clinical use is choice of cut-off value. Related decision making cannot be solely based on statistical criteria. For example, the main clinical focus may be on high PPV (i.e. selection of a patient group that certainly needs prophylaxis) or rather on high NPV (i.e. selection of a patient group where prophylaxis can be safely omitted).

The current study indicates that the efficient identification of patients at high risk of FN continues to face serious challenges. Additional strategies are required for future research before FN risk models can be incorporated into routine clinical practice. As a first step, systematic literature reviews (documenting all currently proposed FN risk factors with supporting evidence), hypothesis-driven reanalyses of existing data, and, where required, well-defined primary data collections should be used to define the most promising elements. These elements should be consistent with our knowledge of the pathophysiology of chemotherapy-induced FN, or at least repeatable in independent clinical studies. Additional criteria would include high predictive ability and easy applicability in routine practice situations. The resulting set of candidate predictors would inform thorough, sufficiently

powered, prospective cohort studies generating comprehensive datasets for risk model generation and validation. Under ideal circumstances, additional clinical and health economic evidence for the resulting prediction models would be obtained from randomized controlled studies comparing standard medical strategies with medical strategies dependent on predicted individual risk [31]. The primary endpoint of FN occurrence should be complemented with secondary endpoints including FN-related mortality and hospitalisation for FN. In the real-world, feasibility aspects and timeliness may require more limited approaches.

It should additionally be noted that even validated risk models would only affect patients' health outcomes if they influenced physicians' treatment decisions [32]. Salar, *et al.* [23] showed that although in the IMPACT NHL population about 60% of the patients were assessed as being at high risk of FN, less than half received primary prophylactic CSF as per guideline recommendations [8-11], indicating that there is an additional risk assessment done by physicians. As some guideline recommendations remain rather vague, risk models could be expected to provide clearer guidance for distinguishing high risk from low risk patients. Even models with limited predictive ability may make physicians more aware of relevant risk criteria. Comparative studies evaluating how the availability of risk models influences physician behaviour and health outcomes [32] might help to promote evidence-driven risk prediction and optimize clinical and supportive care together with physicians' decision making on chemotherapy use, patient surveillance and the need for prophylaxis.

The limited performance of our risk models highlights the importance of careful clinical decision making until validated models are available with adequate predictive ability. Therefore, there is a clear need for further studies and continuing validation of proposed risk predictors and tools.

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M.S., K.L.B. and R.P. designed the research study. M.S. and K.L.B. performed the modelling analysis. All authors analysed and interpreted the data and wrote the paper; M.S. and A.M.P. prepared the first draft. The authors are fully responsible for content and editorial discussion for this manuscript.

DISCLOSURE AND COMPETING INTERESTS

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M.S. receives research funding from Amgen via employment institution and has served on advisory boards for Amgen. K.L.B. is a consultant and contract worker at Amgen Ltd. Z.S. is an employee of Amgen (Europe) GmbH. A.M.P. receives research funding from Amgen via employment institution. R.P. is a consultant in receipt of honoraria from Chugai, Bayer, Roche, and Amgen and has served on advisory boards for Bayer, Amgen and Roche.

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TABLES

Table I: Baseline Demographics and disposition of study population.

	IMPACT NHL (N = 1829)	INC-EU[1] (N = 240)
Tumor Type		
Diffuse large B-cell lymphoma (DLBCL)	1136 (62%)	154 (64%)
Follicular lymphoma (FL)	345 (19%)	35 (15%)
Other	348 (19%)	51 (21%)
Regimen received		
CHOP-14	536 (29%)	41 (17%)
CHOP-21	1293 (71%)	178 (74%)
Other	0	21 (9%)
Planned to receive Rituximab	1698 (93%)	196 (82%)
Number of planned cycles		
≤4 cycles	239 (9%)	51 (21%)
5 - 6 cycles	1027 (56%)	105 (44%)
>6 cycles	563 (31%)	84 (35%)
Age - mean (SD)	60.2 (13.9)	63.2 (12.9)
Age≥65 years	805 (44%)	130 (54%)
Female	803 (44%)	105 (44%)
Ann Arbor Stage 3-4	1142 (62%)	133/237 (56%)
International Prognostic Index (IPI) intermediate/high	849/1484 (57%)	162/237 (68%)
FLIPI intermediate/High	251/345 (73%)	not available
Weight (kg) – mean (SD)	73.9 (15.5)	75 (16)
Prior chemotherapy (chemo- and/or radiotherapy)	143 (8%)	25 (10%)
Low baseline albumin <35 g/dl	254 (14%)	54/188 (29%)
Missing baseline albumin	628 (34%)	52/240 (22%)
Low baseline absolute neutrophil count<3 or WBC<5	377 (21%)	52/237 (22%)
Cardiovascular comorbidities	398 (22%)	65 (27%)

[1] Based on INC-EU dataset and as reported in Pettengell*, et al.* 2009 [16].

Table II: Risk model performance in the INC-EU (training) and IMPACT NHL (external validation) dataset.

	FN in first cycle			**FN in any cycle**		
	INC-EU (training dataset)[1]	IMPACT NHL (validation dataset)	IMPACT NHL (validation dataset)	INC-EU (training dataset)[1]	IMPACT NHL (validation dataset)	IMPACT NHL (validation dataset)
Choice of cut-off	Optimal for INC-EU model	Optimal for INC-EU model	Optimal for IMPACT NHL model	Optimal for INC-EU model	Optimal for INC-EU model	Optimal for IMPACT NHL model
Cut-off value	0.116	0.116	0.014	0.232	0.232	0.089
Correct predictions (%)	192 (80)	1583 (87)	1074 (59)	180 (76)	1306 (78)	1113 (66)
Area under the ROC curve (95% CI)	0.86 (0.79-0.94)	0.64 (0.59-0.69)		0.83 (0.76-0.90)	0.71 (0.68-0.75)	
Sensitivity (%)	81	14	59	76	42	66[2]
Specificity (%)	80	93	59	76	86	67[2]
Negative predictive value (%)	98	93	95	92	87	90
Positive predictive value (%)	28	13	10	48	40	30

CI, confidence interval; FN, febrile neutropenia; ROC, receiver operating characteristic

[1] As published previously (Pettengell*, et al.* 2009 [16]).

[2] Formal criterion for successful validation met.

Table III: INC-EU model of FN risk in first and any cycle – comparison of original model parameters and re-estimated model parameters based on the IMPACT NHL dataset

	FN in first cycle				FN in any cycle			
	Original model parameters[1]		Re-estimated model parameters[2]		Original model parameters[1]		Re-estimated model parameters[2]	
Covariates	Odds ratio (95% CI)	p value[3]	Odds ratio (95% CI)	p value[3]	Odds ratio (95% CI)	p value[3]	Odds ratio (95% CI)	p value[3]
Age[4]	2.20 (1.21-4.01)	0.01	1.16 (0.96-1.41)	0.13	1.79 (1.16-2.78)	0.01	1.43 (1.24-1.65)	< 0.01
Weight[5]	0.62 (0.43-0.89)	0.01	0.89 (0.78-1.03)	0.22	0.62 (0.44-0.88)	0.01	0.90 (0.84-0.98)	0.01
Cardiovascular comorbidity	-		-		2.56 (1.04-6.29)	0.04	1.16 (0.82-1.65)	0.39
Low baseline ANC or WBC[6]	-		-		4.18 (1.82-9.60)	< 0.01	1.92 (1.38-2.67)	< 0.01
Previous chemotherapy	6.39 (1.72-23.68)	<0.01	1.46 (0.79-2.70)	0.22	1.76 (0.49-6.36)	0.39	1.02 (0.61-1.70)	0.94
Planned cyclophosphamide dose[7]	1.16 (1.02-1.32)	0.02	1.12 (0.98-1.27)	0.10	1.33 (1.16-1.52)	< 0.01	1.14 (1.04-1.26)	0.01
Planned cytarabine dose[7]	1.06 (0.98-1.16)	0.15	Not administered in IMPACT NHL		1.09 (1.05-1.13)	<0.01	Not administered in IMPACT NHL	
Planned etoposide dose[7]	1.59 (1.20-2.11)	<0.01			1.27 (1.03-1.57)	0.02		
Dose dense regimen (cycle length 2 weeks)	-		-		1.84 (0.71-4.78)	0.21	2.07 (1.45-2.95)	< 0.01
CSF use before an event occurred[8]	0.18 (0.03-0.94)	0.04	0.48 (0.30-0.77)	0.00	0.21 (0.10-0.44)	< 0.01	0.45 (0.32-0.64)	< 0.01
Dose reduction before an event occurred[8]	-		-		0.24 (0.09-0.63)	< 0.01	0.32 (0.21-0.48)	< 0.01
Dose delay before an event occurred[8]	-		-		0.17 (0.07-0.40)	< 0.01	0.39 (0.28-0.55)	< 0.01
Baseline albumin low[9]	4.76 (1.35-16.71)	0.02	3.15 (1.98-5.01)	0.00	-		-	

Baseline albumin missing[9]	0.52 (0.09-2.99)	0.46	1.54 (0.99-2.39)	0.06	-		-	
Baseline alkaline phosphatase high[10]	-		Not recorded in IMPACT NHL		9.07 (1.41-58.50)	0.02	Not recorded in IMPACT NHL	
Baseline alkaline phosphatase missing[10]	-				4.75 (0.73-30.84)	0.10		
Recent infection[11]	3.07 (0.99-9.52)	0.05			3.32 (1.03-10.71)	0.04		

ANC, absolute neutrophil count; CI, confidence interval; CSF, colony-stimulating factor; WBC, white blood cell count.

[1] Based on INC-EU dataset and as reported in Pettengell*, et al.* 2009 [16]; N = 237 usable observations.

[2] Based on IMPACT NHL dataset; N = 1818 usable observations for cycle 1 models and N = 1675 usable observations for any cycle model.

[3]Based on general estimating equations-based robust standard error estimates allowing for clustering by study site.

[4] Per additional 10 years of age.

[5] Per additional 10 kg body weight.

[6] Baseline ANC < 3.0 x 10^9/l or WBC < 5.0 x 10^9/l.

[7] Per additional mg/m^2 body surface area/week; per additional 50 mg/m^2.

[8] Myelopoietic growth factor use; chemotherapy dose reduction; chemotherapy dose delay before a FN event occurred.

[9] Baseline albumin <35 g/dl, missing category introduced to avoid loss of observations

[10] Baseline alkaline phosphatase > 250 iU/l, missing category introduced to avoid loss of observations

[11] During 60 d prior to chemotherapy or ongoing infectious comorbidity